Recent Advances in Indian Herbal Drug Research

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Current Status of Herbal Drugs in India: An Overview

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Received 19 September, 2006; Accepted 6 December, 2006

Summary Herbal drugs constitute a major share of all the officially recognised systems of health in India viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy, except Allopathy. More than 70% of India's 1.1 billion population still use these non-allopathic systems of medicine. Currently, there is no separate category of herbal drugs or dietary supplements, as per the Indian Drugs Act. However, there is a vast experiential-evidence base for many of the natural drugs. This offers immense opportunities for Observational Therapeutics and Reverse Pharmacology. Evidence-based herbals are widely used in the diverse systems and manufactured, as per the pharmacopoeial guidelines, by a well-organised industry. Significant basic and clinical research has been carried out on the medicinal plants and their formulations, with the state-of-the-art methods in a number of Institutes/Universities. There are some good examples. Indian medicinal plants also provide a rich source for antioxidants that are known to prevent/delay different diseased states. The antioxidant protection is observed at different levels. The medicinal plants also contain other beneficial compounds like ingredients for functional foods. Hence, the global knowledge about Ayurveda and Indian herbals will hopefully be enhanced by information on the evidence-base of these plants. This will yield rich dividends in the coming years.

Key Words: Ayurveda, Indian medicinal plants, reverse pharmacology, observational therapeutics, antioxidant

Introduction

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of health *viz*. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. These systems have rightfully existed sideby-side with Allopathy and are not in 'the domain of obscurity', as stated by Venkat Subramanian [1]. Millions of Indians use herbal drugs regularly, as spices, home-remedies, health foods as well as over-the-counter (OTC) as self-medication or also as drugs prescribed in the non-allopathic systems [2]. The more than 500,000 non-allopathic practitioners are trained in the medical colleges (>400) of their respective systems of health and are registered with the official councils which monitor professionalism. Hence, these systems are

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not folklore or traditional herbal practices. There are basic axioms of these systems leading to a logical and systematic structure of pathogenesis and diagnosis, which serves also as a determinant for therapy [3].

The developer of a potent natural product penicillin, Nobel-laureate Ernst Boris Chain wrote an inspiring article entitled "The quest for new biodynamic substances". In 1967, he wrote, "In China and India there has been an extensive drive aimed at the systemic study of medicinal plants traditionally used in these countries in folklore medicine; this has failed, so far, to bring to light new classes of compounds with interesting pharmacologic activities. As far as drug research is concerned, therefore, we cannot expect many major surprises to come from the study of plant constituents" [4]. The current overview would disprove the infallibility of this Nobel laureate, by giving examples of novel activities of Indian medicinal plants.

Observational Therapeutics and Reverse Pharmacology

India, having a pluralistic healthcare system, offers an unfettered choice for the quest for new clinical effects of traditionally used medicinal plants [5]. Roy Chaudhary coined a neologism for such a discipline—Observational Therapeutics [6]. He expressed his hope that further research directed at a few of the chronic diseases against which more drugs are needed, such as diabetes, bronchial asthma, could lead to the discovery of new drugs for these conditions. Observational Therapeutics is an antecedent of the path of Reverse Pharmacology for new natural drug development. Reverse Pharmacology was proposed and initiated by Vaidya [7]. Reverse Pharmacology is possible only in those countries with pluralistic healthcare and where robust clinical and

laboratory documentation of novel human, pharmacodynamic effects are possible by inter-system collaborative teamwork [8]. India, at the national level, has adopted this approach of Reverse Pharmacology and also the golden triangular research for correlating the three fields by R & D network *viz*. modern medicine, Indian systems of medicine, and life and pharmaceutical sciences [9]. Reverse Pharmacology is defined as the science of integrating documented clinical/experiential hits, into leads by transdisciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research. The identification of structures with novel biodynamic effects can also lead to new chemical entity path for drug development.

The scope of Reverse Pharmacology is to understand the mechanisms of action at multiple levels of biological organization and to optimise safety, efficacy and acceptability of the leads in natural products, based on relevant science.

Research Approach to Herbal Products

The path of Reverse Pharmacology, arising from Observational Therapeutics is complementary to other approaches for natural drug development (Fig. 1).

The diversity of medical uses of plant is at times daunting for a new entrant to the field. But for a multidisciplinary research and a development network the options of research approach provide deep motivation for identification of new pharmacophores. Besides expanding the herbal therapeutic and preventive armamentarium, new pharmacophores may help to evolve new targets of drug action as well as a possibility for combinatorial chemistry on the novel pharmacophores. For example, curcumin has been a target molecule for a significant endeavour for a large number of combinatorial compounds. The Council of Scientific and Industrial Research

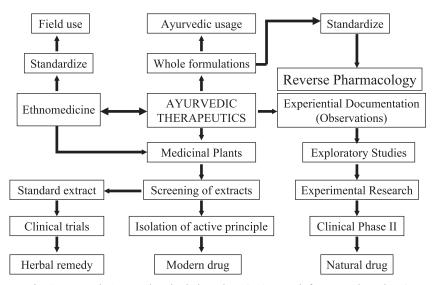


Fig. 1. Research Approach to herbal products(R & D Path for Natural Products)

(CSIR), in India has initiated sizeable and meaningful efforts for the development of herbal-based formulations for diabetes, arthritis and hepatitis by a national network programme [8]. The industry, the academia and the government research laboratories work in close collaboration. Interesting and novel activities have been detected with the selected plants and some of the active ingredients of therapeutically demonstrable effects e.g. glycaemic control and inhibition of HbA1c (glycosylated haemoglobin) level coupled with a reduction in *in vitro* formation of Amadori products.

The diverse approaches to herbal drugs have led to interesting hits and novel activities, which need further in depth drug development efforts, both as herbal as well as new single molecule drugs. Table 1 lists the activity of ten of the interesting Ayurvedic drugs [10–19].

Literature on Indian medicinal plants

There is vast literature on Ayurveda in Sanskrit, Hindi and regional languages that is often not accessible to the other language groups. The monographs and books in English are also available. But sometimes there are errors in translating the technical Sanskrit and Indian words into English. It is desirable that prior to embarking on developing any Indian herbal drug, the original Sanskrit textbooks or the experts and scholars of Ayurveda are properly consulted. There have been many scientific reviews on Indian medicinal plants too. Table 2 lists some of the highly recommended books, monographs and reviews that can be used as per the needs of the reader [20–45]. There has been an ongoing major CSIR effort of digitizing the traditional Ayurvedic knowledge library (TKDL).

Institutions/Centres Working on Indian Medicinal Plants

A large number of academic, industrial and government institutes are conducting research on the medicinal plants of India. There has been no systematic review of the massive work that is available from this nation. Many international data-bases and web-sites do not cover even the work published in the Indian Journals. Hence, there is a global lack of awareness of the mass and nature of work carried out on diverse aspects *viz*. ethnobotany, phytochemistry, pharmacognosy, pharmacology, clinical trials, safety studies and formulation-research. Table 3 provides a short list of some of the eminent institutes which are active in research on medicinal plants and in Ayurveda.

Use and Potential of Selected Indian Plants

Since ancient times a number of Indian medicinal plants have been used globally. There are many references to Indian medicinal plants and trade in spices in a number of historical documents. For instance, Indian aloe is very widely used in India for cosmetic, medicinal and nutraceutical purposes [46]. But the antiaging effects of the pickled preparations are unique [47, 48]. Despite the global reputation of aloe in dermato-cosmetics, the potential as antiaging is still untapped. Similarly, the plant Adhatoda vasica has been extensively studied for cough and the active principles have been known [49]. However, the potential for use in bleeding disorders and tuberculosis is untapped. Table 4 cites the clinical uses and the therapeutic potential of 14 selected Indian medicinal plants [50-99]. There is a need for an international collaborative effort to explore, on a fast track, the hits provided by clinical observations of astute physicians.

Reverse Pharmacology on these selected plants may lead

Table 1.	Activity	of interesting	Ayurvedic drugs
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No	Sanskrit Name	Botanical Name	Activity	Status	Medline hits	Google hits	Key reference
1	Amalaki	Phyllanthus emblica	Antiaging	A	69	71000	[10]
2	Ashwagandha	Withania somnifera	Phytoestrogen	В	176	162000	[11]
3	Atmagupta	Mucuna pruriens	Parkinsonism	D	53	155000	[12]
4	Bilva	Aegle marmelos	Irritable Bowel	A	51	63300	[13]
5	Brahmi	Centella asiatica	Cognition	C	136	478000	[14]
6	Daruharidra	Berberis aristata	Antimicrobial	C	15	58500	[15]
7	Eranda	Ricinus communis	Anti inflammatory	A	2146	665000	[16]
8	Nimba	Azadirachta indica	Anti malarial	A	333	342000	[17]
9	Shunthi	Zingiber officinalis	Anti nausea	В	368	266000	[18]
10	Yashtimadhu	Glycyrrhiza glabra	Anti ulcer	C	161	396000	[19]

^{*} A = Widespread and safe usage, B = Dietary supplements, C = Evidence based, D = IND-NDA (Investigate New Drug—Natural Drug Application)

Table 2. Recommended literature on Indian medicinal plants

Title words	Target readership	Special strength	Reference
Ayurveda & Modern Medicine	Allopathy doctors	Correlates Life Sciences	[20]
Selected Medicinal Plants	Regulatory Pharmacists	Readable short monographs	[21]
Ayurvedic Pharmacology	Ayurveda students	Dosage & usage	[22]
Indigenous Drugs of India	Phyto-research	Pharmacological action	[23]
Indian Herbal Pharmacopoeia	Manufacturer & quality control	Analytical methods	[24]
Ayurvedic Pharmacopoeia	Standardization	Official methods	[25]
Home remedies	Lay readers	Simple users	[26]
Wealth of India	Herbal Scientist	Tremendous information	[27]
Medicinal Plants of India	Medical Scientist	Research opportunities	[28]
Indian Medicinal Plants	Botanist & Pharmacists	Details of plants	[29]
Pharmacognosy of Indigenous Drugs	Pharmacognosists	Morphology	[30]
Compendium	Phytochemists	Chemical structures	[31]
Ayurveda Revisited	Phyto-scientists	Novel approaches	[32]
Current Research	Pharmacologists	Periodic reviews	[33, 34]
Ethnovet Heritage	Veterinarians	Research Potential	[35]
Clinically Useful Drugs	Practicing herbalists	Formulations & properties	[36]
The Herbs of Ayurveda	Phyto-scientists	Excellent pictures	[37]
Indian Herbal Remedies	Ayurvedic research	Indications summary	[38]
Cultivation and Utilization	Phyto-scientists	Excellent reviews	[39]
Antioxidants	Immunopharmacology	Excellent review	[40]
Future drugs	Drug developers	Novel paths	[41]
Pharmacology of plants	Pharmacologists	Rasayana focus	[42]
Ayurvedic concepts	Physicians	Current relevance	[43]
Ayurvedic plants	Information scientists	Database	[44]
Level of evidence	Clinical pharmacologist	Use-strengths	[45]

not only to new leads and drug candidates but also to novel targets and pharmacodynamic efforts. For example, investigations on *Coleus forskohlii*, used as pickles in some parts of India, led to isolation of forskolin, with multifaceted effects. The latter were mediated by activation of adenylate cylase and increased concentration of cyclic adenosine monophosphate (cAMP) [100]. Subsequently, forskolin (Fig. 2) has served as a very important tool in molecular pharmacology and endocrinology.

There are cAMP-independent effects of forskolin *viz*. through modulation of nicotinic acetylcholine receptor channel desensitization, modulation of voltage-gated potassium channels, reversal of multidrug resistance etc. [99]. This example suggests the complexity of effects of even simple phytomolecules. Hence, the emphasis has to be primarily on the human effect, as documented in Observational Therapeutics.

Indian Medicinal Plants as a Source of Antioxidants and Radical Scavengers

In recent years, there is a tremendous interest in the possible role of nutrition in prevention of disease. In this

context, antioxidants, especially derived from natural sources such as Indian medicinal plants and herbal drugs derived from them, require special attention. Antioxidants neutralize the toxic and 'volatile' free radicals. Antioxidants have many potential applications, especially in relation to human health, both in terms of prevention of disease and therapy [101, 102]. In biological systems oxygen gives rise to a large number of free radicals and other reactive species collectively known as 'reactive oxygen species' (ROS). Another group of reactive species are termed as 'reactive nitrogen species' (RNS) [103, 104]. In a normal healthy human, the generation of ROS and RNS are effectively kept in check by the various levels of antioxidant defense. However, when the humans get exposed to adverse physiochemical, environmental or pathological agents this delicately maintained balance is shifted in favour of pro-oxidants resulting in oxidative stress [101]. Cellular damage induced by oxidative stress has been implicated in the etiology of a large number (>100) of human diseases as well as the process of ageing. Various antioxidants may prevent and/or improve diseased states [101, 103, 105, 106]. These include the intracellular antioxidant enzymes and the dietary or oral

Table 3. Herbal Research institute/centres in India

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Name	City	Postal code	e-mail
CCRAS(Central Council for Research in Ayurveda and Siddha)	New Delhi	110001	ccras_dir1@nic.in
RRL (Regional Research Laboratory) (CSIR)	Jammu-Tawi	180001	qazi_gn@yahoo.com
NBRI (National Botanical Research Institute) (CSIR)	Lucknow	226001	r.tuli@nbri.res.in
Gujarat Ayurveda University	Jamnagar	361008	info@ayurveduniversity.com
Bhavan's SPARC	Mumbai	400049	bhaspa@bom5.vsnl.net.in
National Institute of Ayurveda	Jaipur	302002	nia@raj.nic.in
ACARTS	Mumbai	400008	clinpharm@hathway.com
Arya Vaidya Shala	Kottakal	676503	mail@aryavaidyasala.com
Interdisciplinary School of Health Sciences	Pune	411007	shs@unipune.ernet.in
Banaras Hindu University	Vanarasi	221005	directorims@satyam.net.in
CIMAP (Central Institute for Medicinal and Aromatic Plants)	Lucknow	226015	director@cimap.res.in
ICMR (Indian Coucil for Medical Research)	New Delhi	110029	icmrhqds@sansad.nic.in
National Medicinal Plants Board	New Delhi	110001	ccras_dir1@nic.in
Indian Drug Manufacturers	Mumbai	400018	publications@idmaindia.com
Regional Medical Research Centre (ICMR)	Belgaum	590010	oicrmrcblm@yahoo.co.in
PERD Centre (Pharmaceutical Education and Research Development)	Ahmedabad	380054	perd@perdcentre.com
CCRUM (Central Council for Research in Unani Medicine)	New Delhi	110001	ccrum@del3.vsnl.net.in
NISCOM(National Institute of Science Communication)	New Delhi	110012	niscom@sirnetd.ernet.in
IMPCOPS (Indian Medical Practitoners Co-operative Pharmacy & Stores Ltd.)	Chennai	600041	admin@webhealthcenter.com
IHMMR (Indian Institute of History of Medicine and Medical Research)	New Delhi	110062	root@hamduni.ren.nic.in
Zandu Foundation	Mumbai	400025	zanduho@giasbm01.vsnl.net.in
Pharmexcil	Hyderabad	500038	info@pharmexcil.com
Chemexcil	Mumbai	400039	chemexcil@vsnl.com
CDRI (Central Drug Researech Institute) (CSIR)	Lucknow	226001	icmrrcdi@ ren.nic.in
IMPLANT Centre (Inter-university Medicinal Plant Laboratory for Analysis, Nurture and Therapeutics)	Rajkot	360005	rrkalariya@sauuni.ernet.in
NIMHANS (National Institute for Mental health and Neurosciences)	Bangalore	560029	sidda@nimhans.kar.nic.in
Panjab University	Chandigarh	600014	webman@puchd.ac.in
LM College of Pharmacy	Ahmedabad	380009	mukeshgohel@hotmail.com
NBPGR (National Bureau of Plant Genetic Resources)	New Delhi	110012	root@nbpgr.delhi.nic.in
NPRC (Nicholas Piramal Research Centre)	Mumbai	400013	recruitment@nicholaspiramal.co.
NCL (National Chemical Laboratory)	Pune	411008	rs.malge@ncl.res.in
TBGRI (Tropical Botanical Garden & Research Institute)	Thiruvantpuram	695562	director_tbgri@rediffmail.com
BHU (Banaras Hindu University)	Varanasi	221005	vc_bhu@sify.com
Podar Hospital	Mumbai	400018	rapamc@rediffmail.com
Botanical Survey of India	Kolkata	700001	envis@cal2.vsnl.net.in
FRHLT (Foundation for Revitalisation of Local Health Traditions)	Bangalore	560024	Darshan.shankar@frlht.org.in
IASTAM (International Association for the Study of Traditional Asian Medicine)	Mumbai	400012	iastamindia@vsnl.net
ADMA (Ayurvedic Drug Manufacturing Association)	Mumbai	400012	amam2003@sify.com

Table 4. Use and potential of selected Indian plants

Plant name	Commonest Ayurvedic usage	References	Therapeutic potential	References
Adhatoda vasica	Kasashwasaghna (Antitussive)	[50, 51]	Antituberculosis, Haemostatic	[52–54]
Aloe vera	Kushtghna (Skin diseases), Agnidagdha vrana (Burns)	[55–57]	Antidiabetic	[58, 59]
Boswellia serrata	Shothaghna (Anti inflammatory), Grahaghna (Anti spasmodic)	[60–63]	Immunomodulator	[64, 65]
Centella asiatica	Smritiprada (Memory- enhancing), Kushtaghna (Skin diseases)	[66–68]	Antiaging	[69, 70]
Curcuma longa	Pramehaghna (Anti-diabetic), Kandooghna (Anti pruritic), Vranapaha (Wound healing)	[71–74]	Cancer Prevention	[75]
Leptadenia reticulata	Stanya (Galactogogue)	[76]	Anticonjunctivitis	[77]
Mucuna pruriens	Vrushya (Aphrodisiac)	[78]	Antiparkinsonism	[<i>79</i>]
Ocimum sanctum	Pratishyayahara (Anti cold)	[80]	Anticancer	[81, 82]
Picrorrhiza kurroa	Kamalahara (Anti-jaundice)	[83]	Lipid-lowering	[84]
Piper longum	Shwasakasahara (Anti asthamatic)	[85]	Antimalarial	[86]
Pterocarpus marsupium	Mehaghna (Anti-diabetic)	[87, 88]	Antiinflammatory	[89]
Terminalia chebula	Anulomana (Mild laxative)	[90, 91]	Medhya	[92]
Tribulus terrestris	Ashmarighna (Litholytic)	[93]	Antiprostatism	[94]
Trigonella foenum- graecum	Medoghna (Lipid lowering), Stanya (Galactogogue)	[95, 96]	Antidiadetic	[97, 98]

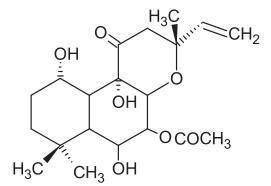


Fig. 2. Forskolin (7β-acetoxy-8, 13-epoxy-1, 6β, 9-trihydroxy-labd-14-en-11-one)

supplements in the form of vitamin C, vitamin E, β -carotene, zinc and selenium [107, 108]. Antioxidants also can act at different levels of protection such as prevention, interception and repair.

Indian medicinal plants provide a rich source of antioxidants. A review of literature shows that there are over 40 Indian medicinal plants showing antioxidant abilities at various levels of protection (Table 5). The medicinal plants that show significant antioxidant activity include *Acacia* catechu, Achyranthes aspera, Aegle marmelos (Bengal quince, Bel), Aglaia roxburghiana (Priyangu), Allium cepa (Onion), Allium sativum, Aloe vera, Amomum subulatum, Andrographis paniculata, Asparagus racemosus, Azadirachta indica, Bacopa monniera, Bauhinia purpurea, Brassica campastris, Butea monosperma, Camellia sinensis, Capparis decidua, Capsicum annum, Centella asiatica, Cinnamomum verum, Commiphora mukul, Crataeva nurvala, Crocus sativus, Curcuma longa, Cymbopogan citrates, Emblica officinalis, Emilia sonchifolia, Garcinia atroviridis, Garcinia kola, Glycyrrhiza glabra, Hemidesmus indicus, Hypericum perforatum, Indigofera tinctoria, Melissa officinalis, Momordica charantia, Morus alba, Murraya koenigii, Nigella sativa, Ocimum sanctum, Picrorrhiza kurroa, Piper beetle, Plumbago zeylanica, Premna tomentosa, Punica granatum, Rubia cordifolia, Sesamum indicum, Sida cordifolia, Swertia decursata, Syzigium cumini, Terminalia arjuna, Terminalia bellarica, Tinospora cordifolia, Trigonella foenum-graecum, Withania somnifera and Zingiber officinalis [109–111]. There are also a number of ayurvedic formulations containing ingredients from medicinal plants that show antioxidant activities. These are Abana, Amrita bindu, Cphycocyanin, Centalaplus, Chapparal, Geriforte, Jigrine, Liv-52, Maharishi formulations, Muthu marunthu, Ophtacare, P55A, Sandhika, Student rasayana and Tamra bhasma. There are still a large number of plants and ayurvedic formulations whose antioxidant activities need to be examined in relation to their potential therapeutic and related beneficial properties. More recent assays also should be included to study the antioxidant properties of medicinal plants or their chemical constituents. This will greatly help in identifying more potent compounds with potential applications in prevention

Table 5. Indian medicinal plants and levels of antioxidant action

<u>Level 1</u> : Suppression of radical formation	Cassia occidentalis, Crocus sativus, Emblica officinalis, Hemidesmus indicus, Indigofera tinctoria, Momordica charantia, Murraya koenigii, Ocimum sanctum, Picrorhiza kurroa, Sida cordifolia, Spirulina fusiformis, Tinospora cordifolia, Vinca rosea, Withania somnifera & Zingiber officinale
<u>Level 2</u> : Scavenging of primary radicals	Acacia catechu, Aloe vera, Butea monosperma, Crocus sativus, Curcuma longa, Hippophae rhamnoides, Indigofera tinctoria, Momordica charantia, Ocimum sanctum, Plumbago zeylanica, Psoralea corylifolia, Rotula aquatica & Swertia decussata
Level 3: Scavenging of secondary radicals	Allium sativum, Allium cepa, Aloe vera, Amaranthus blitum, Argemon maxicana, Asparagus racemosus, Azadirachta indica, Curcuma longa, Emblica officinalis, Glycyrrhiza glabra, Hemidesmus indicus, Mangifera indica, Momordica charantia, Murraya koenigii, Ocimum sanctum, Onosoma echioides, Picrorhiza kurroa, Piper betel, Plumbago zeylanica, Psoralea corylifolia, Sesamum indicum, Sida cordifolia, Swertia decussata, Terminalia bellarica, Tinospora cordifolia, Vinca rosea, Withania somnifera & Zingiber officinale
<u>Level 4</u> : Reconstitution of membranes	Allium sativum, Aloe vera, Camellia sinensis, Curcuma longa, Argemon maxicana, Cassia occidentalis, Crocus sativus, Emblica officinalis, Ocimum sanctum, Tinospora cordifolia, Vinca rosea, Withania somnifera & Zingiber officinale
Level 5: Repair of damage	Ocimum sanctum &, Hibiscus sabdariffa

and/or therapy of human ailments. Newer approaches utilizing collaborative research and modern technology in combination with established traditional health principles will yield rich dividends in the near future in improving health, especially among people who do not have access to the use of costlier western systems of medicine.

Indian Medicinal Plants as a Source of Other Beneficial Compounds

These medicinal plants are also important source of other type of beneficial compounds including the ingredients for functional foods. These functional foods promote better health to prevent chronic illness. Some ingredients that make food functional are dietary fibres, vitamins, minerals, antioxidants, oligosaccharides, essential fatty acids (omega-3), lactic acid bacteria cultures and lignins. Many of these are present in medicinal plants. Indian systems of medicine believe that complex diseases can be treated with complex combination of botanicals unlike in the West, with single drugs. Whole foods are hence used in India as functional foods rather than supplements. Some medicinal plants and dietary constituents having functional attributes are spices such as onion, garlic, mustard, red chilli, turmeric, clove, cinnamon, saffron, curry leaf, fenugreek and ginger. Some herbs such as Bixa orellana and vegetables like amla, wheat grass, soybean and Garcinia cambogia have antitumor effects [112, 113]. Other medicinal plants with such functional properties include Aegle marmelos, Allium cepa, Aloe vera, Andrographis paniculata, Azadirachta indica and Brassica juncea [111, 114].

Conclusion and Future Prospects

In India more than 70% of the population use herbal drugs

for their health. There is a vast experience-based evidence for many of these drugs. There are also a number of Institutes/ Universities in India carrying our research on herbal drugs and medicinal plants. Using 'reverse pharmacological' approach, several Institutes carry out basic and clinical research on the potential health benefits of herbal drugs. There are many successful examples in this direction. These herbal drugs and Indian medicinal plants are also rich sources of beneficial compounds including antioxidants and components that can be used in functional foods. Newer approaches utilizing collaborative research and modern technology in combination with established traditional health principles will yield rich dividends in the near future in improving health, especially among people who do not have access to the use of costlier western systems of medicine.

Acknowledgments

We thank Dr. Shridhar Anishetty and Mr. Rajkumar Mishra for their help in preparation of the overview.

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